Long-term use of combination DMARDs did not sustain disease remissions, but delayed joint damage in early rheumatoid arthritis

Korpela M, Laasonen L, Hannonen P, et al. **Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study.** Arthritis Rheum. 2004;50:2072-81.

QUESTION

In patients with early rheumatoid arthritis (RA), is a combination of disease-modifying antirheumatic drugs (C-DMARDs) better than single DMARDs (S-DMARDs) for sustaining long-term disease remissions and slowing the deterioration of joint damage?

METHODS

Design: Randomized controlled trial (Finnish Rheumatoid Arthritis Combination Therapy [FIN-RACo] trial).
Allocation: Unclear concealment.*
Blinding: Blinded {outcome assessor}†.*
Follow-up period: 5 years.
Setting: {18 hospitals in Finland}†.
Patients: 199 patients (mean age 47 y, 64% women) with RA of recent onset (< 2 y, median 6 mo) who had never received DMARDs, had ≥ 3 swollen joints, and had at least 3 of an erythrocyte sedimentation rate ≥ 28 mm/h or a C-reactive protein level > 19 mg/L, morning stiffness ≥ 29 minutes, > 5 swollen joints, and > 10 tender joints. {Exclusion criteria included previous DMARD use, glucocorticoid use in the past 2 weeks, serious comorbid conditions, history of cancer, and pregnancy or potential for pregnancy}†.
Intervention: Patients were allocated to C-DMARDs (sulfasalazine, 500 mg twice daily; methotrexate, 7.5 mg/wk; hydroxychloroquine, 300 mg/d; and prednisolone, 5 mg/d, with adjustments allowed to achieve remission) (n = 97) or to an S-DMARD (sulfasalazine, 2 to 3 g/d [or methotrexate, or azathioprine], with or without prednisolone) (n = 98). After 2 years, the choice of DMARD and prednisolone was unrestricted.
Outcomes: Remission (defined by American College of Rheumatology criteria), extent of radiologic damage in the joints of the hands and feet (using Larsen scores 0 to 210, higher scores = greater damage), adverse events, and reconstructive joint surgery.
Patient follow-up: 89% at 2 years, and 80% at 5 years (intention-to-treat analysis).

MAIN RESULTS

After 2 years, 90% of the C-DMARD group continued to receive DMARD combinations and 62% of the S-DMARD group switched to DMARD combinations. More patients achieved remission in the C-DMARD group than the S-DMARD group at 2 years (Table), but the difference was not sustained at 5 years (Table). At 5 years, both groups had an increase in Larsen score, but to a lesser extent in the C-DMARD group (median increase in Larsen score 14 vs 20, P = 0.004). The groups did not differ for frequency of reconstructive surgery (P = 0.17) or adverse events.

CONCLUSION

In patients with early rheumatoid arthritis, long-term use of combination disease-modifying antirheumatic drugs did not sustain disease remissions at 5 years but improved radiologic outcomes.

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For correspondence: Dr. M. Korpela, Tampere University Hospital, Tampere, Finland. E-mail markku.korpela@pshp.fi. ■

*See Glossary.

†**Mottonen T, Hannonen P, Leirisalo-Repo M, et al.** Lancet. 1999;353:1568-73.

Combination disease-modifying antirheumatic drug therapy (C-DMARD) vs single DMARD therapy (S-DMARD) for early rheumatoid arthritis at 2 to 5 years*

Outcome	Follow-up	C-DMARD	S-DMARD	RBI (95% CI)	NNT (CI)
Remission	2 y	40%	18%	129% (39 to 284)	5 (3 to 11)
	5 y	28%	22%	28% (25 to 120)	Not significant

*Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

The therapeutic pyramid has guided RA treatment for decades (a progression from monotherapy to triple therapy). Since the introduction of methotrexate in the late 1980s, a trend toward earlier and more aggressive therapy or a combination of therapies for RA has emerged (1). In the 1990s, the benefit of combination therapy with methotrexate, sulfasalazine, and antimalarials was seen. Side effects of these combinations have remained problematic, however.

Early, aggressive therapy can improve function and reduce inflammation, radiologic damage, loss of function, and mortality (2). The study by Korpela and colleagues confirmed these findings in a study with avoidance of therapeutic alternatives and a high follow-up rate.

However, the therapeutic pyramid is still in our hands. How many excellent trials are needed to change our treatment algorhythm? In 2004, the Study of New Onset Rheumatoid Arthritis (SONORA) (with a large inception cohort of patients with RA) showed that 40% of these patients had not taken DMARDs after 1 year and 22% had not taken DMARDs after 2 years, despite good clinical status in only 7% of patients (3). In 2003, 2 studies showed that therapy adjusted for disease activity was helpful in treating early and established disease as aggressively as needed (4, 5). The continuation of early and aggressive therapy throughout the patient's lifetime might sustain this clinical benefit.

Oliver Sander, MD
University Hospital Düsseldorf
Düsseldorf, Germany

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